Detecting undetectables: Can conductances of action potential models be changed without appreciable change in the transmembrane potential?

Journal club

Will An

Introduction – Action Potential (AP) model

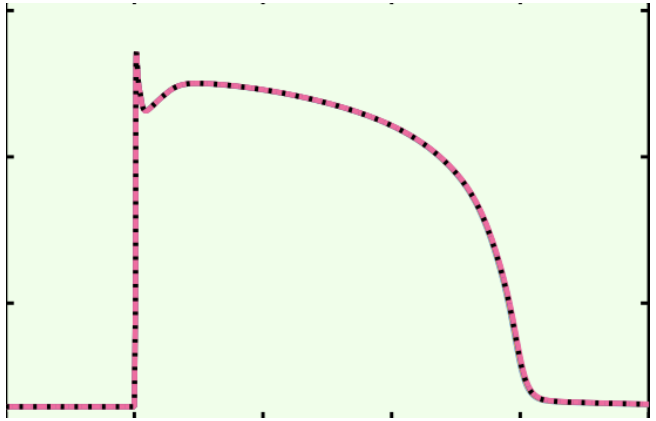
- AP model is to simulate the transmembrane potential of cardiac cell
- Generally controlled by the two simplified equations below:
  - $$\frac{dv(t)}{dt} = -\sum_{i=1}^{N} I_i(v, s), \qquad I_i = g_i o_i (v - v_i^0),$$
    - s: gate variables
    - g_i: maximum conductance
    - I_i: gate open probability
- For every different I_i we have different parameter g_i

a: I_{Na}
b: I_{to}
c: I_{CaL}
d: I_{Ks}
e: I_{pK}
f: I_{NaK}
g: I_{Kr}
h: I_{NaCa}
i: I_{K1}
j: I_{bCa}
k: I_{pCa}
l: I_{bNa}

Introduction – Action Potential (AP) model

- Some parameters are insensitive: if we slightly change them, the sum of currents or AP does not change much.
- For example, if we perturb conductance of background Na.
- $g_{bNa} \rightarrow (1+\epsilon) g_{bNa}$

$$\frac{dv(t)}{dt} = -\sum_{i=1}^{N} I_i(v,s), \qquad I_i = g_i o_i (v - v_i^0),$$



Perturbed g_{bNa}

Default g_{bNa}

Introduction – Action Potential (AP) model

- This paper tried to find insensitive conductance parameters.
- It can be single one: g_i
- Or a combination: $\{g_i, g_j, g_k\}$

- It used Singular Value Decomposition (SVD) to find them.

Method – Matrix representation

- Before applying SVD, it first stored the currents for each time step into a matrix A

$$A = \begin{pmatrix} I_1^1 & \cdots & I_N^1 \\ \vdots & & \vdots \\ I_1^M & \cdots & I_N^M \end{pmatrix}$$

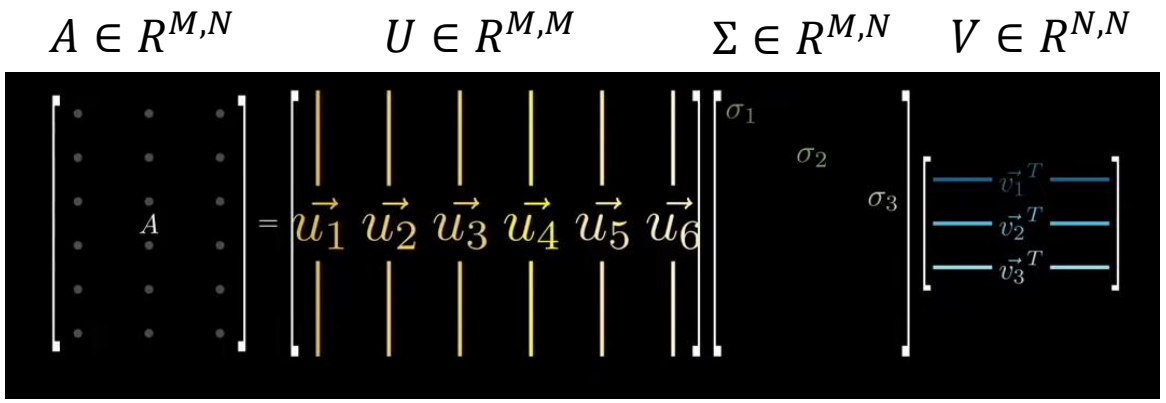
  - where I_j^k means current I for ion j at time $t_k = k\Delta t$.
  - $A \in R^{M,N}$
  - $M = \#\ of\ time\ steps; N = \#\ of\ ion\ currents$
- Then in unperturbed case, we have:
  - $I_T = I_{total} = A\mu,\ where\ \mu = (1,1,\dots,1)^T$ and $\mu \in R^{N,1}$
- For perturbed case
  - $g_1 \to (1+\epsilon)g_1$, then $\bar{\mu} = (1+\epsilon, 1, \dots, 1)^T$
- The total current is given by:

$$I_T = \begin{pmatrix} I_T^1 \\ I_T^2 \\ \vdots \\ I_T^M \end{pmatrix}$$

Method – SVD

- Singular Value Decomposition can decompose any matrix into three matrix.
- $\forall\, A \in R^{M,N}, A = U\Sigma V^T$

- $\overrightarrow{u_i}$: left singular vectors
- σ_i: singular values
- $\overrightarrow{v_i}$: right singular vectors



- Some properties of SVD
- $\sigma_i = 0\ if\ i > r$
- $A\overrightarrow{v_i} = \sigma_i \overrightarrow{u_i},\ i = 1, \dots, r$
- $A\overrightarrow{v_i} = 0,\ i = r+1, \dots, N$
  - Where r is the rank of matrix *A*
- $\{v_1, v_2, \dots, v_N\}$ is an orthonormal basis.

Method – Perturbation effect on currents

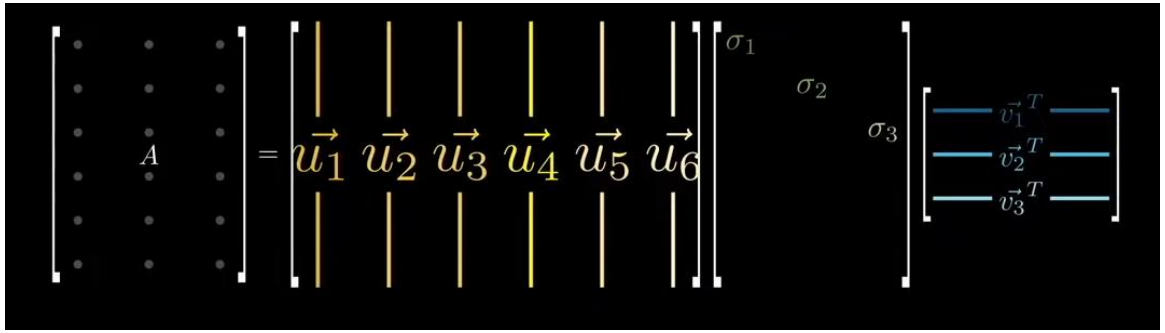
- Now consider a specific perturbation $\bar{\mu} = \mu + \epsilon v_i$
- $I_T = A\mu,\ \bar{I}_T = A\bar{\mu}, A\overrightarrow{v_i} = \sigma_i \overrightarrow{u_i}$

$$I_T - \bar{I}_T = A\mu - A\bar{\mu} = -\varepsilon A v_i = -\varepsilon\sigma_i u_i$$

$$\|I_T - \bar{I}_T\|^2 = (I_T - \bar{I}_T, I_T - \bar{I}_T) = \varepsilon^2\sigma_i^2(u_i, u_i) = \varepsilon^2\sigma_i^2$$

  - where (u_i, u_i) *is the inner product of* u_i, *and is one*

$A \in R^{M,N}$ $U \in R^{M,M}$ $\Sigma \in R^{M,N}$ $V \in R^{N,N}$



- Finally: $\left|\left|I_T - \bar{I}_T\right|\right| = \epsilon\sigma_i$
- Meaning if we have a small singular value σ_i, that perturbing direction is insensitive.

Method – Perturbation effect on currents

- Finally: $\left|\left|I_T - \bar{I}_T\right|\right| = \epsilon\sigma_i$
- But this perturbation only lies on certain direction v_i

- For example, if $v_i = \left(\frac{1}{\sqrt{2}}, \frac{1}{\sqrt{2}}, 0, 0, \ldots, 0\right)^T$, we only perturbed g_1, g_2 by $\frac{\epsilon}{\sqrt{2}}$
- So, what if we want to discuss all possible perturbations of $\{g_i\}$?

Method – Perturbation effect on currents

- So, what if we want to discuss all possible perturbations of $\{g_i\}$?

- Since $\{v_1, v_2, \dots, v_N\}$ is an orthonormal basis.
- Now consider any perturbation $\bar{\mu} = \mu + \sum_{i=1}^{N} \epsilon_i v_i\,,\ N = \#\ of\ ion\ currents$

$$I_T - \bar{I}_T = A\mu - A\bar{\mu} = -\sum_{i=1}^{N} \varepsilon_i \sigma_i u_i,$$

$$\|I_T - \bar{I}_T\|^2 = \sum_{i=1}^{N} \varepsilon_i^2 \sigma_i^2 = \sum_{i=1}^{r} \varepsilon_i^2 \sigma_i^2.$$

  - $\sigma_i = 0\ if\ i > r$
- In other words, if perturbation can be expressed using only the singular vectors $\{v_i\}_{i=r+1}^{N}$, $\left|\left|I_T - \bar{I}_T\right|\right| = 0$, such a perturbation will not lead to changes in the total membrane current.
- Or we can say perturbation in $span\{v_{r+1}, \dots, v_N\}$ is unidentifiable

Method – Identifiability index (current)

- Perturbation in $span\{v_{r+1}, \dots, v_N\}$ is unidentifiable

- Can we quantify the sensitiveness/identifiability of the perturbation unit vector?
- Consider any perturbation unit vector e:

$$e = \sum_{i=1}^{N} (e, v_i) v_i.$$

- And the projection of e onto $span\{v_{r+1}, \dots, v_N\}$:

$$P_N e = \sum_{i=r+1}^{N} (e, v_i) v_i.$$

- Identifiability index of a vector to be given by:

$$k(e) = \|e - P_N e\|.$$

Method – Identifiability index (current)

- Perturbation in N $= span\{v_{r+1}, \dots, v_N\}$ is unidentifiable $P_N e = \sum_{i=r+1}^{N} (e, v_i) v_i.$
- Identifiability index of a vector to be given by:

$$k(e) = \|e - P_N e\|.$$

- If $k(e) = 1$:
  - $P_N e = 0$, meaning part of the vector that cannot be identified = 0
  - Perturbation in direction e is identifiable
- If $k(e) = 0$:
  - $P_N e = 1$, meaning e is in $span\{v_{r+1}, \dots, v_N\}$
  - Perturbation in direction e is unidentifiable

Method – Identifiability index (AP)

- The identifiability index is got by transmembrane current.

$$\|I_T - \bar{I}_T\|^2 = \sum_{i=1}^{N} \varepsilon_i^2 \sigma_i^2 = \sum_{i=1}^{r} \varepsilon_i^2 \sigma_i^2.$$

- This paper also calculates another identifiability index based on measuring the difference between the computed AP in the default version and a perturbed version of the model

- It defines H to measure the perturbation effect on AP

$$H(\varepsilon, v_i) = \sum_{q=1}^{5} H_q(\varepsilon, v_i),$$

Method – Identifiability index (AP)

- It defines H to measure the perturbation effect on AP

$$H_1(\varepsilon, v_i) = \frac{|\mathrm{APD}_{30}(v^*) - \mathrm{APD}_{30}(\bar{v}(\varepsilon \cdot v_i))|}{|\mathrm{APD}_{30}(v^*)|},$$

$$H_2(\varepsilon, v_i) = \frac{|\mathrm{APD}_{50}(v^*) - \mathrm{APD}_{50}(\bar{v}(\varepsilon \cdot v_i))|}{|\mathrm{APD}_{50}(v^*)|},$$

$$H_3(\varepsilon, v_i) = \frac{|\mathrm{APD}_{80}(v^*) - \mathrm{APD}_{80}(\bar{v}(\varepsilon \cdot v_i))|}{|\mathrm{APD}_{80}(v^*)|},$$

$$H_4(\varepsilon, v_i) = \frac{\left|\left(\frac{dv^*}{dt}\right)_{\max} - \left(\frac{d\bar{v}(\varepsilon \cdot v_i)}{dt}\right)_{\max}\right|}{\left|\left(\frac{dv^*}{dt}\right)_{\max}\right|},$$

$$H_5(\varepsilon, v_i) = \frac{\|v^* - \bar{v}(\varepsilon \cdot v_i)\|}{\|v^*\|}.$$

$$H(\varepsilon, v_i) = \sum_{q=1}^{5} H_q(\varepsilon, v_i),$$

$$S = \mathrm{span}\{v_i\} \text{ for } i \text{ such that } \left\{ \max_{-0.5 \le \varepsilon \le 0.5} H(\varepsilon, v_i) < \delta \right\}.$$

Method – Identifiability index (AP)

- It defines H to measure the perturbation effect on AP

$$H(\varepsilon, v_i) = \sum_{q=1}^{5} H_q(\varepsilon, v_i),$$

- Perturbation in S is unidentifiable ($\delta = 0.25$, is the threshold value)

$$S = \text{span}\{v_i\} \text{ for } i \text{ such that } \left\{ \max_{-0.5 \le \varepsilon \le 0.5} H(\varepsilon, v_i) < \delta \right\}.$$

$$k(e) = \|e - P_S e\|,$$

- If $k(e) = 1$:
  - $P_N e = 0$, meaning part of the vector that cannot be identified = 0
  - Perturbation in direction e is identifiable
- If $k(e) = 0$:
  - $P_N e = 1$, meaning e is in $span\{v_{r+1}, \dots, v_N\}$
  - Perturbation in direction e is unidentifiable

Result - Tusscher model

- Tusscher model:

$$\frac{dV}{dt} = -\frac{I_{ion} + I_{stim}}{C_m}$$

$$I_{ion} = I_{Na} + I_{K1} + I_{to} + I_{Kr} + I_{Ks} + I_{CaL} + I_{NaCa} + I_{NaK} + I_{pCa} + I_{pK} + I_{bCa} + I_{bNa}$$

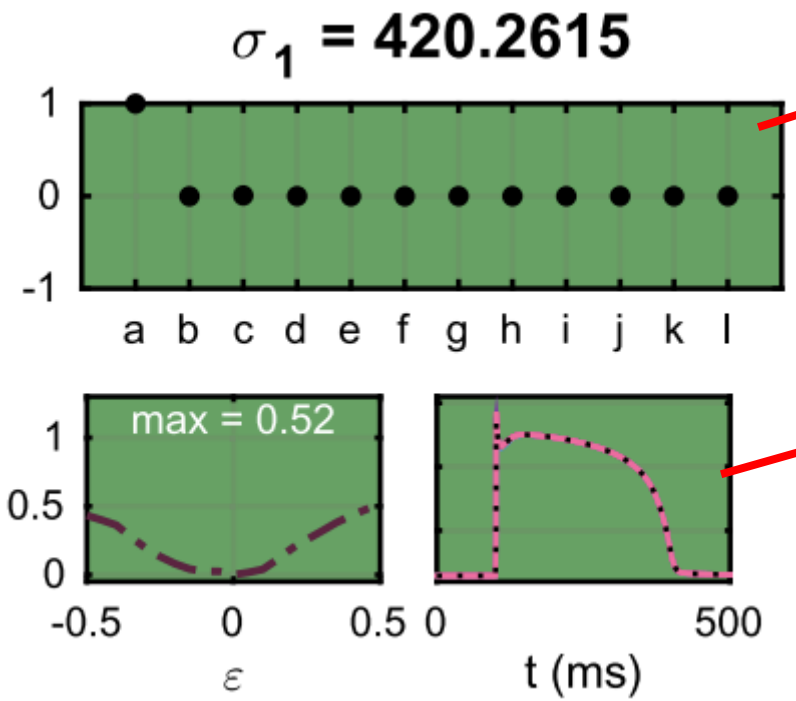
- It perturbed the model by singular vectors
- Record currents every $\Delta t = 0.1ms$

Result - Tusscher model (I_{Na})

- Perturbation by $v_1 = (1,0,\dots,0)^T$
- Meaning I_{Na} is multiplied by a factor $1 + 1\epsilon$
- Or we can say $g_{Na} \rightarrow (1+\epsilon)g_{Na}$

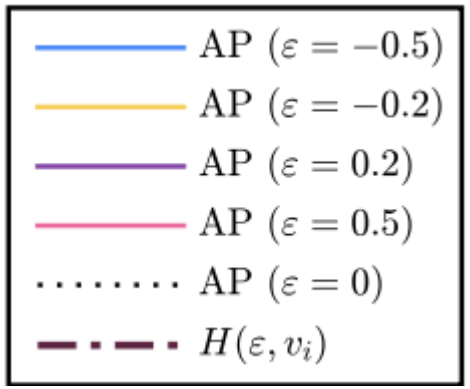
$$I_i = g_i o_i (v - v_i^0),$$

Currents (identifiability)	
a: I_{Na}	(1)
b: I_{to}	(0.95)
c: I_{CaL}	(0.88)
d: I_{Ks}	(0.83)
e: I_{pK}	(0.62)
f: I_{NaK}	(0.32)
g: I_{Kr}	(0.3)
h: I_{NaCa}	(0.18)
i: I_{K1}	(0.16)
j: I_{bCa}	(0.06)
k: I_{pCa}	(0.057)
l: I_{bNa}	(0.02)



Singular vector or Perturb vector

Perturb effect H

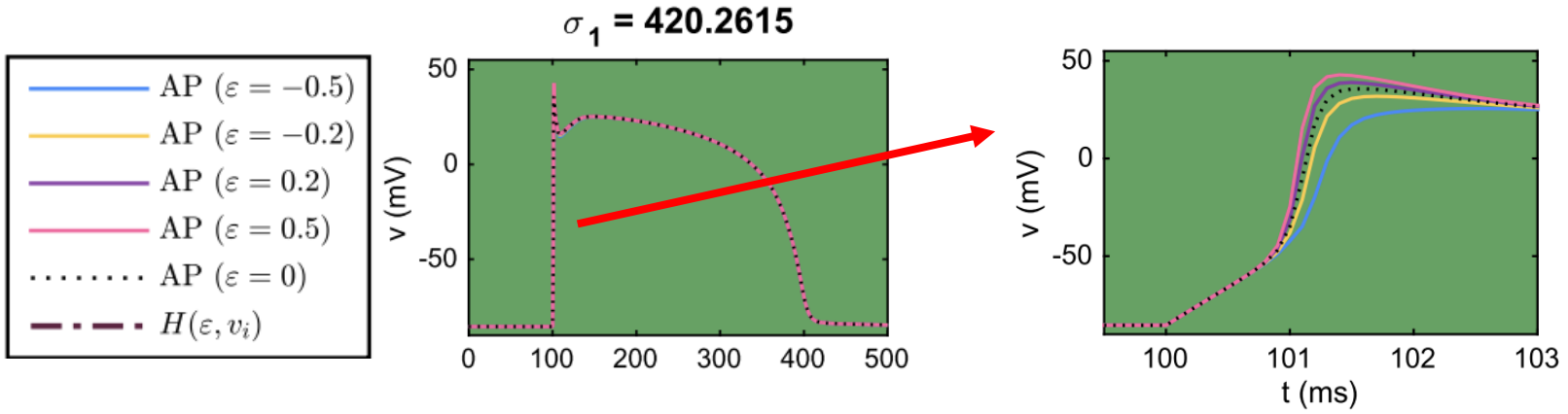


We can see g_{Na} or I_{Na} is quite identifiable

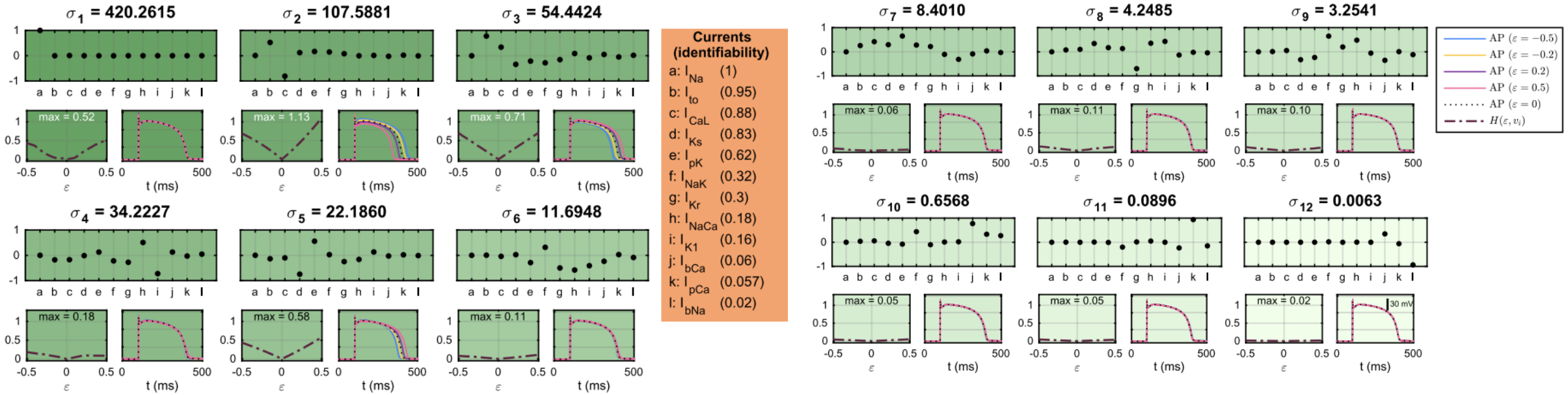
Result - Tusscher model (I_{Na})

- You may wonder why for I_{Na} has a large H but almost same AP for different perturbation ϵ
- That is because fast sodium current I_{Na} actives mainly during upstroke of AP
  - Where H mainly comes from H_4
  - It measures the maximal upstroke velocity

$$H_4(\varepsilon, v_i) = \frac{\left|\left(\frac{dv^*}{dt}\right)_{\max} - \left(\frac{d\bar{v}(\varepsilon \cdot v_i)}{dt}\right)_{\max}\right|}{\left|\left(\frac{dv^*}{dt}\right)_{\max}\right|},$$

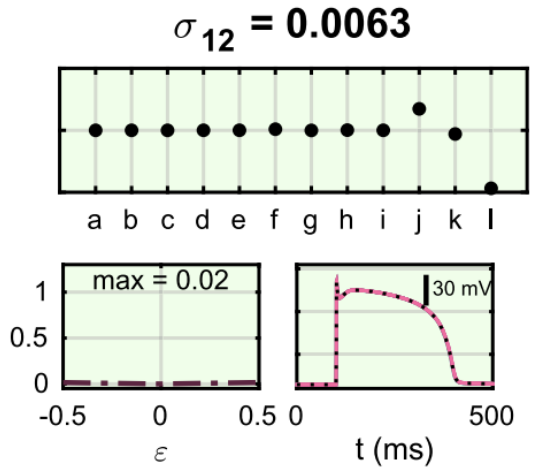


Result - Tusscher model

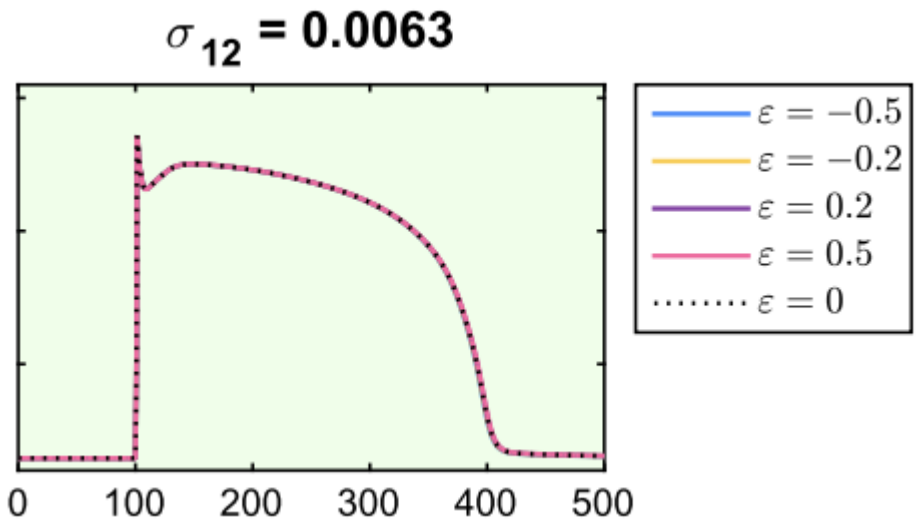


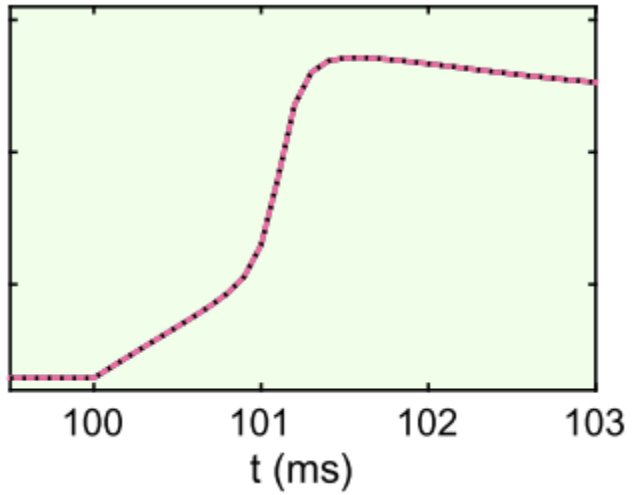
Result - Tusscher model (I_{bCa}, I_{bNa})

- For increasing g_{bCa} decreasing g_{bNa} combination,
- the perturbation is quite unidentifiable.

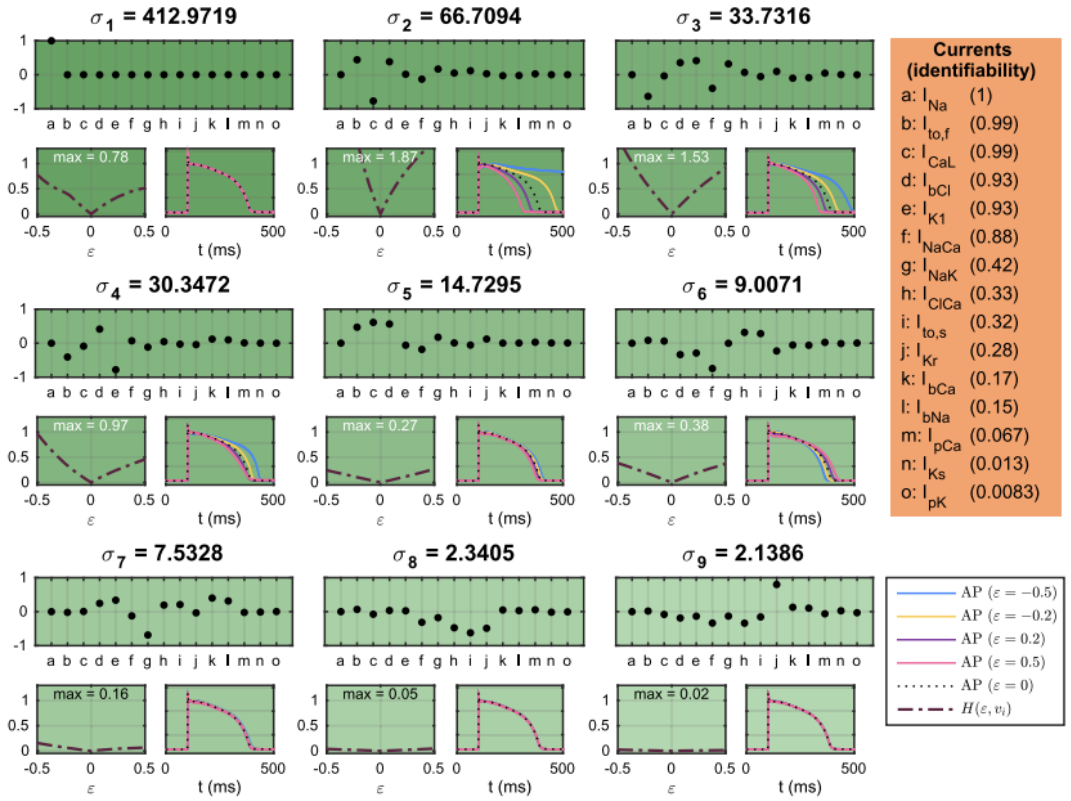


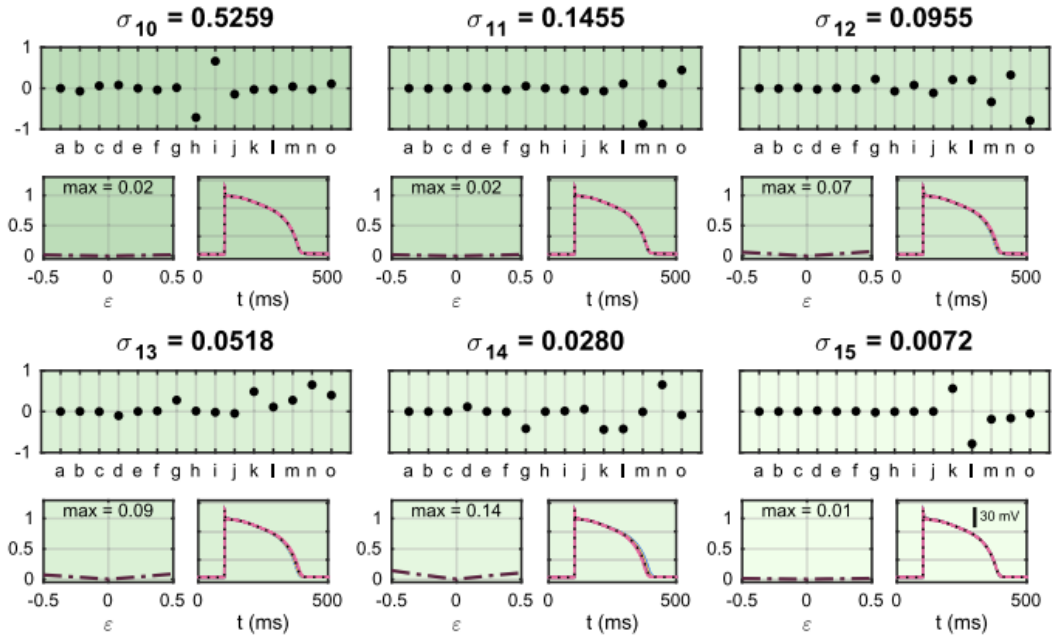
Currents (identifiability)	
a: I_{Na}	(1)
b: I_{to}	(0.95)
c: I_{CaL}	(0.88)
d: I_{Ks}	(0.83)
e: I_{pK}	(0.62)
f: I_{NaK}	(0.32)
g: I_{Kr}	(0.3)
h: I_{NaCa}	(0.18)
i: I_{K1}	(0.16)
j: I_{bCa}	(0.06)
k: I_{pCa}	(0.057)
l: I_{bNa}	(0.02)



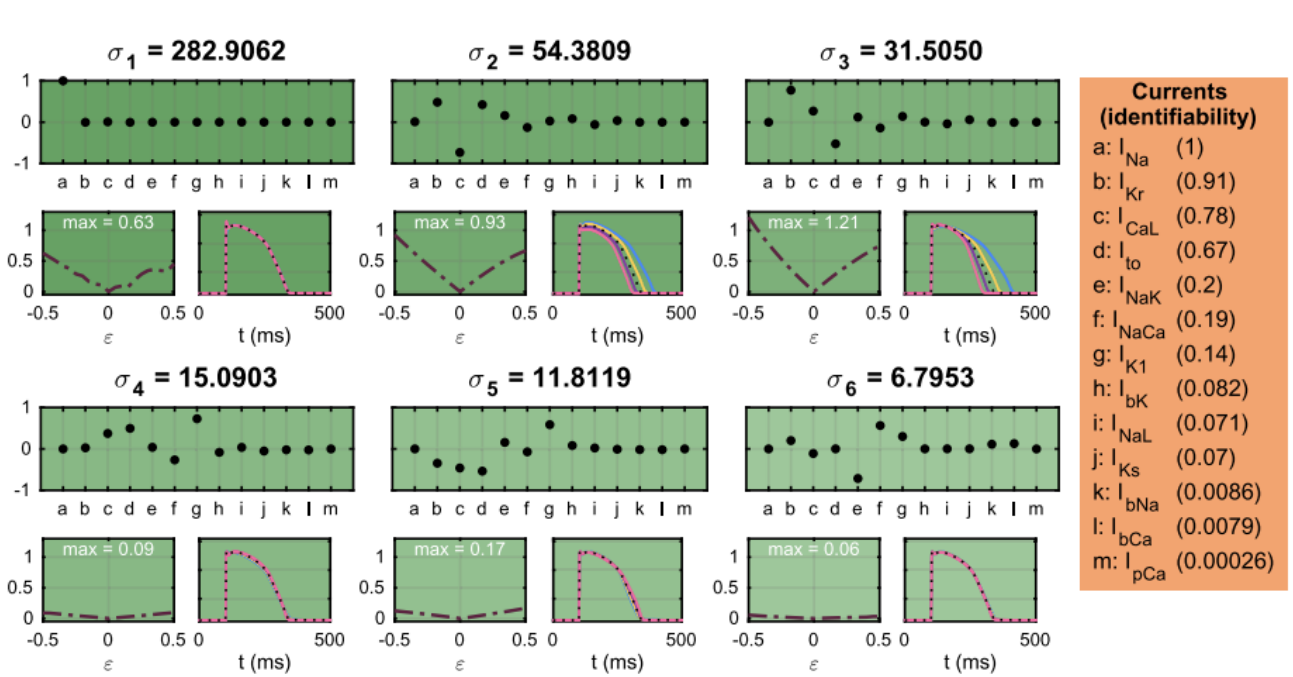


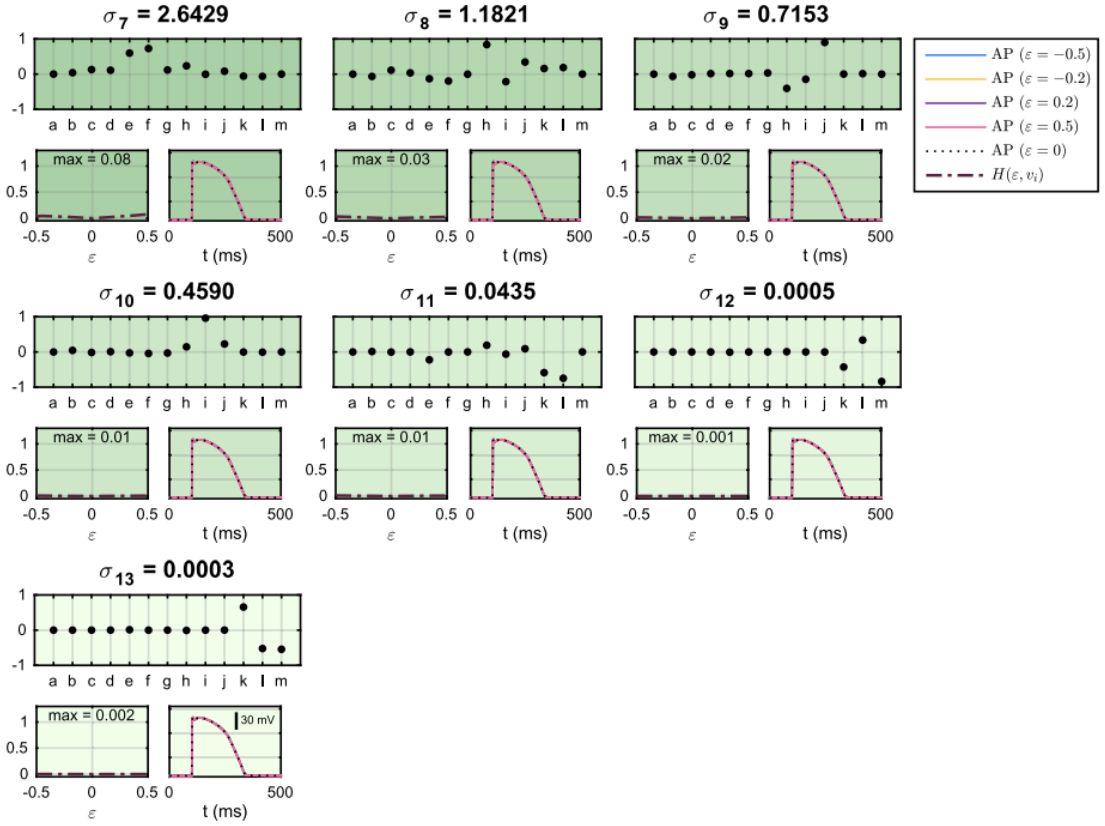
Result - Grandi model





Result - O'Hara model





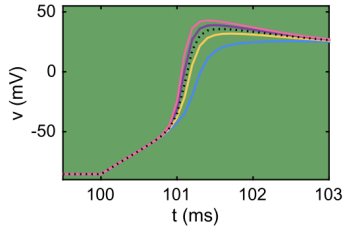
Result - Time step effect (Tusscher)

- When it tried to record the current, a default time step $\Delta t = 0.1ms$ was used.

$$A = \begin{pmatrix} I_1^1 & \cdots & I_N^1 \\ \vdots & & \vdots \\ I_1^M & \cdots & I_N^M \end{pmatrix}$$

- But what if we have a different time step.

- When increasing Δt
  - Largest and smallest singular value decrease
  - But their ratio remains
  - Identify index for I_{Na} decrease a lot
    - This is because the upstroke is less than 2 ms, so $\Delta t \sim O(1\text{ms})$ cannot record it properly



Δt (ms)	0.01	0.1	1	2
σ_1	1309.9	420.3	138.1	24.7
σ_{12}	0.02	0.0063	0.0018	0.0012
σ_{12}/σ_1	1.5×10^{-05}	1.5×10^{-05}	1.3×10^{-05}	4.9×10^{-05}
Identifiability index				
I_{Na}	1.00	1.00	0.002	0.002
I_{to}	0.95	0.95	0.95	0.95
I_{CaL}	0.88	0.88	0.88	0.88
I_{Ks}	0.83	0.83	0.83	0.83
I_{pK}	0.62	0.62	0.62	0.61
I_{NaK}	0.32	0.32	0.32	0.31
I_{Kr}	0.30	0.30	0.30	0.30
I_{NaCa}	0.18	0.18	0.19	0.19
I_{K1}	0.16	0.16	0.15	0.15
I_{bCa}	0.06	0.06	0.06	0.06
I_{pCa}	0.06	0.06	0.06	0.06
I_{bNa}	0.02	0.02	0.02	0.02

Result - Time step effect (Grandi and O'Hara)

Grandi

Δt (ms)	0.01	0.1	1	2
σ_1	1333.8	413.0	330.3	15.0
σ_{15}	0.023	0.0072	0.0018	0.00021
σ_{15}/σ_1	1.7×10^{-05}	1.7×10^{-05}	5.3×10^{-06}	1.4×10^{-05}
Identifiability index				
I_{Na}	1.00	1.00	1.00	0.97
$I_{to,f}$	0.99	0.99	0.99	0.99
I_{CaL}	0.99	0.99	0.99	0.99
I_{bCl}	0.93	0.93	0.93	0.93
I_{K1}	0.93	0.93	0.93	0.93
I_{NaCa}	0.88	0.88	0.88	0.87
I_{NaK}	0.42	0.42	0.42	0.42
I_{ClCa}	0.33	0.33	0.34	0.34
$I_{to,s}$	0.32	0.32	0.32	0.32
I_{Kr}	0.28	0.28	0.29	0.29
I_{bCa}	0.17	0.17	0.17	0.18
I_{bNa}	0.15	0.15	0.14	0.15
I_{pCa}	0.07	0.07	0.07	0.07
I_{Ks}	0.01	0.01	0.01	0.02
I_{pK}	0.01	0.01	0.01	0.22

O'Hara

Δt (ms)	0.01	0.1	1	2
σ_1	894.5	282.9	88.9	88.7
σ_{13}	0.00098	0.00031	8.7×10^{-05}	1.9×10^{-05}
σ_{13}/σ_1	1.1×10^{-06}	1.1×10^{-06}	9.8×10^{-07}	2.1×10^{-07}
Identifiability index				
I_{Na}	1.00	1.00	1.00	1.00
I_{Kr}	0.91	0.91	0.91	0.91
I_{CaL}	0.78	0.78	0.78	0.77
I_{to}	0.67	0.67	0.68	0.68
I_{NaK}	0.20	0.20	0.20	0.20
I_{NaCa}	0.19	0.19	0.19	0.19
I_{K1}	0.14	0.14	0.14	0.14
I_{bK}	0.08	0.08	0.08	0.08
I_{NaL}	0.07	0.07	0.07	0.07
I_{Ks}	0.07	0.07	0.07	0.07
I_{bNa}	0.01	0.01	0.01	0.01
I_{bCa}	0.01	0.01	0.01	0.01
I_{pCa}	0.0003	0.0003	0.0003	0.0003

Result – Drug effect

Tusscher

	No drug	Verapamil $0.5 \cdot g_{CaL}$, $0.75 \cdot g_{Kr}$	Cisapride $0.5 \cdot g_{Kr}$
Identifiability index			
I_{Na}	1.00	1.00	1.00
I_{to}	0.95	0.98	0.95
I_{CaL}	0.88	0.92	0.88
I_{Ks}	0.83	0.85	0.87
I_{pK}	0.62	0.21	0.64
I_{NaK}	0.32	0.35	0.32
I_{Kr}	0.30	0.43	0.14
I_{NaCa}	0.18	0.16	0.14
I_{K1}	0.16	0.28	0.15
I_{bCa}	0.06	0.10	0.05
I_{pCa}	0.06	0.04	0.06
I_{bNa}	0.02	0.03	0.02

Grandi

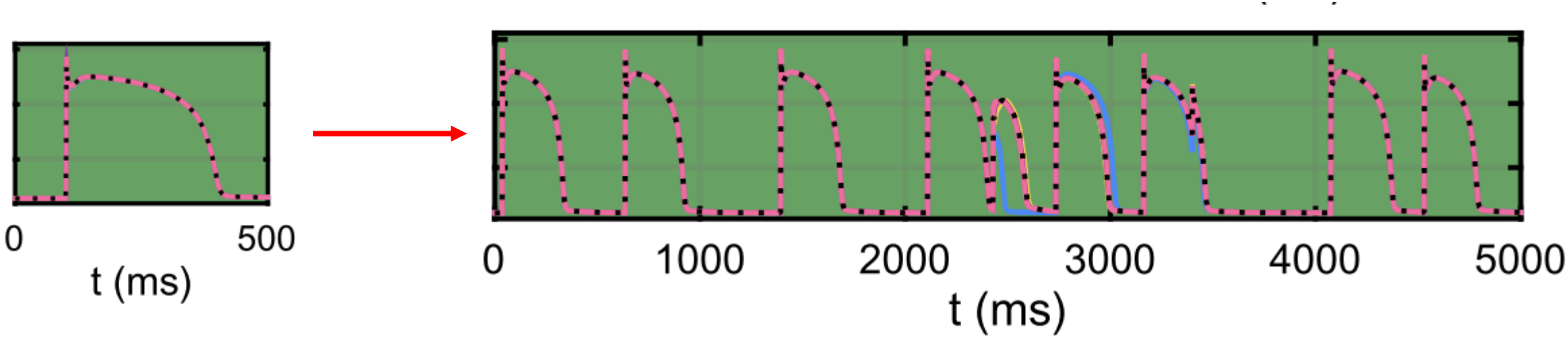
	No drug	Verapamil $0.5 \cdot g_{CaL}$, $0.75 \cdot g_{Kr}$	Cisapride $0.5 \cdot g_{Kr}$
Identifiability index			
I_{Na}	1.00	1.00	1.00
$I_{to,f}$	0.99	0.99	0.99
I_{CaL}	0.99	0.99	0.99
I_{bCl}	0.93	0.90	0.98
I_{K1}	0.93	0.89	1.00
I_{NaCa}	0.88	0.43	0.89
I_{NaK}	0.42	0.39	0.81
I_{ClCa}	0.33	0.05	0.39
$I_{to,s}$	0.32	0.17	0.37
I_{Kr}	0.28	0.11	0.14
I_{bCa}	0.17	0.17	0.44
I_{bNa}	0.15	0.14	0.35
I_{pCa}	0.07	0.06	0.07
I_{Ks}	0.01	0.006	0.02
I_{pK}	0.01	0.005	0.01

O'Hara

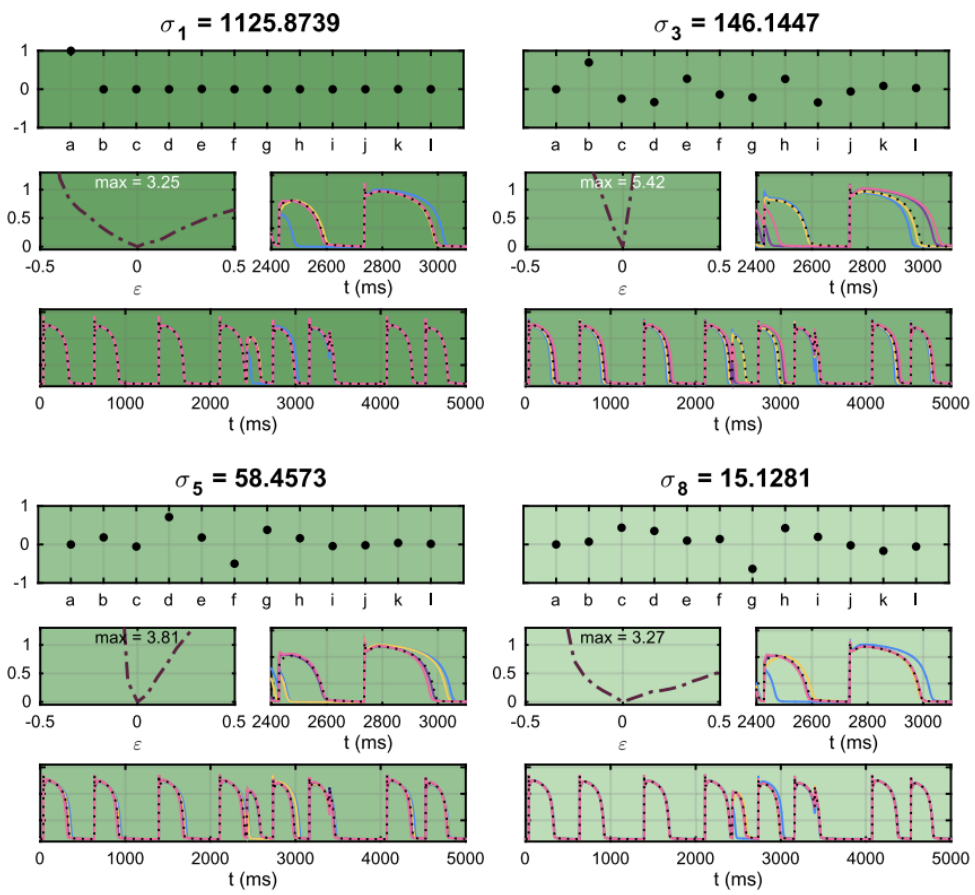
	No drug	Verapamil $0.5 \cdot g_{CaL}$, $0.75 \cdot g_{Kr}$	Cisapride $0.5 \cdot g_{Kr}$
Identifiability index			
I_{Na}	1.00	1.00	1.00
I_{Kr}	0.91	0.97	0.90
I_{CaL}	0.78	0.97	0.92
I_{to}	0.67	1.00	0.90
I_{NaK}	0.20	0.26	0.32
I_{NaCa}	0.19	0.22	0.27
I_{K1}	0.14	0.98	0.54
I_{bK}	0.08	0.17	0.15
I_{NaL}	0.07	0.12	0.10
I_{Ks}	0.07	0.10	0.20
I_{bNa}	0.01	0.02	0.01
I_{bCa}	0.01	0.02	0.01
I_{pCa}	0.0003	0.0003	0.0004

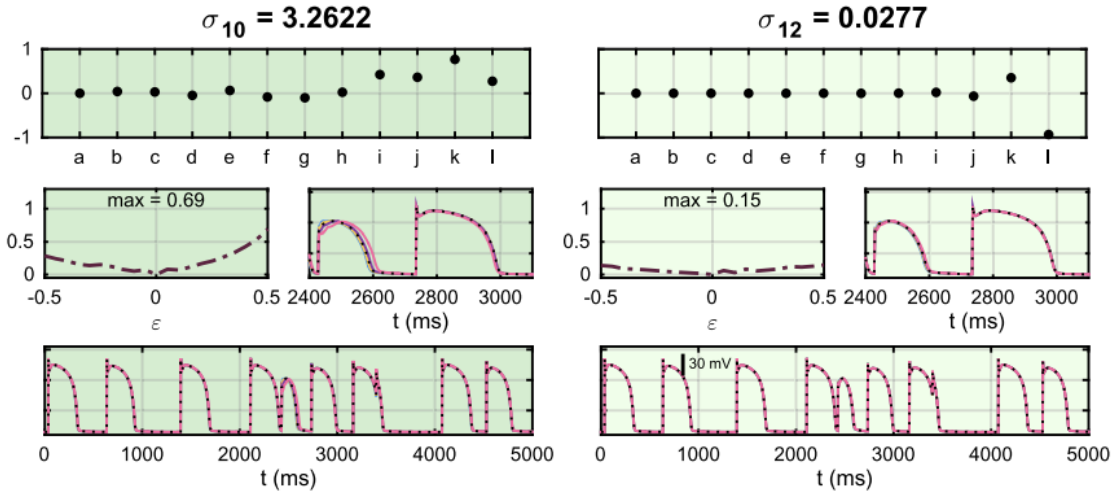
Result – Random stimulation protocol

- Random stimulation protocol is applied to increase the identifiability index.
- Instead of recording one stimulus of AP, here it records several additional stimulus (35.7 ms, 634.9 ms, 1392.5 ms, 2108.8 ms, 2426.9 ms, 2734.4 ms, 3161.8 ms, 3398.7 ms, 4073.6 ms and 4529.0 ms).



Result - Random stimulation (Tusscher)





For reason of space, this paper does not show all singular values here

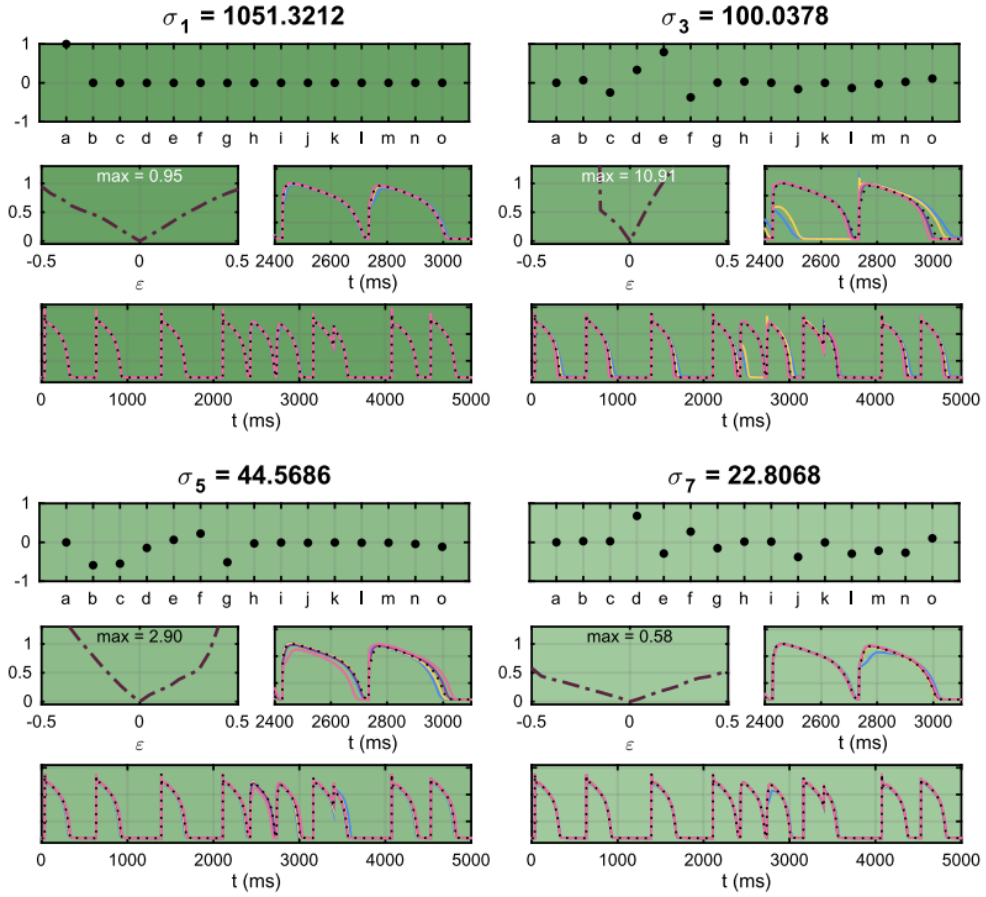
We can see that the perturbation effect H and identify index are increased

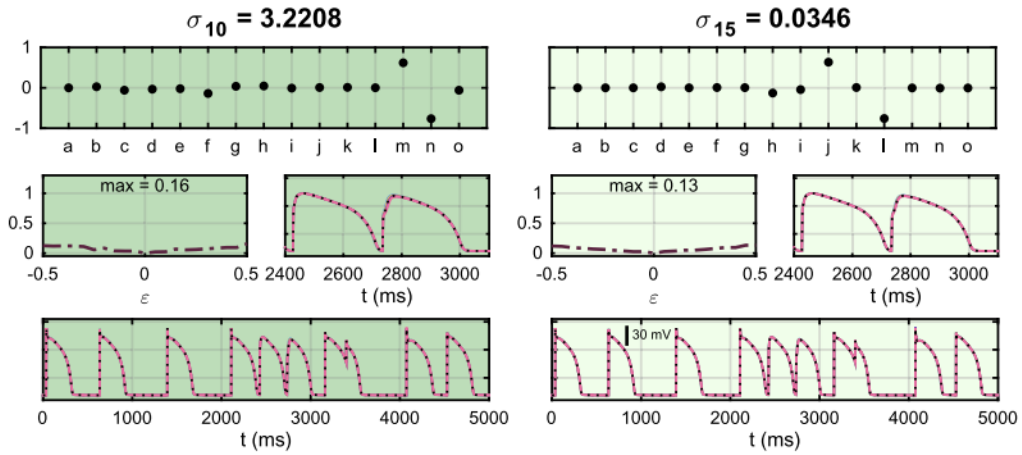
Currents (identifiability)	
a: I_{Na}	(1)
b: I_{to}	(0.95)
c: I_{CaL}	(0.88)
d: I_{Ks}	(0.83)
e: I_{pK}	(0.62)
f: I_{NaK}	(0.32)
g: I_{Kr}	(0.3)
h: I_{NaCa}	(0.18)
i: I_{K1}	(0.16)
j: I_{bCa}	(0.06)
k: I_{pCa}	(0.057)
l: I_{bNa}	(0.02)

Random stimulation →

Currents (identifiability)	
a: I_{Na}	(1)
b: I_{to}	(1)
c: I_{K1}	(1)
d: I_{Ks}	(1)
e: I_{CaL}	(1)
f: I_{pK}	(1)
g: I_{Kr}	(1)
h: I_{NaCa}	(1)
i: I_{NaK}	(1)
j: I_{pCa}	(1)
k: I_{bCa}	(0.94)
l: I_{bNa}	(0.36)

Result - Random stimulation (Grandi)





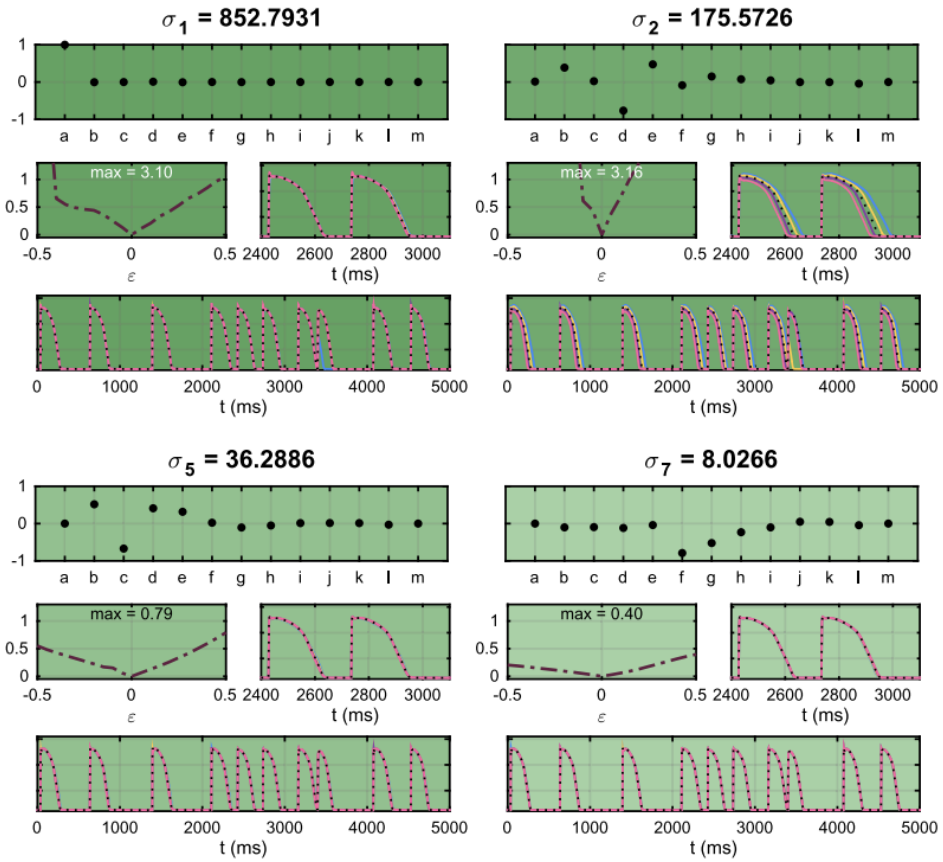
We can see that the perturbation effect H and identify index are increased

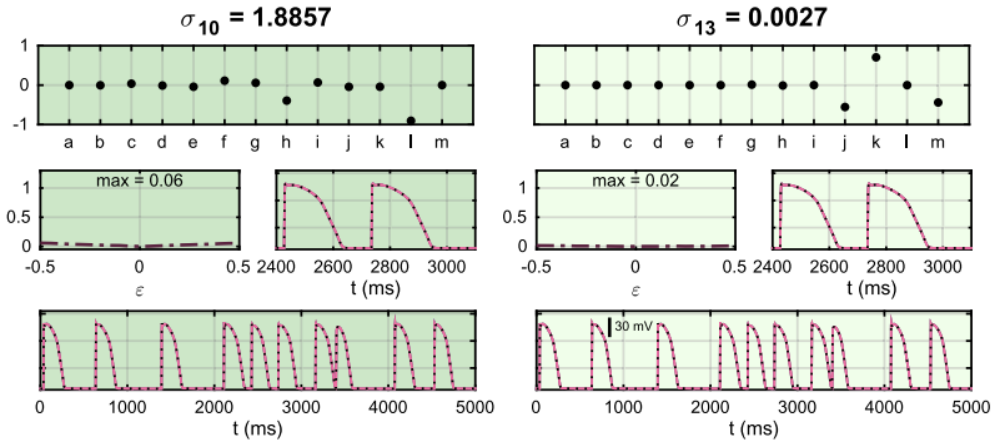
Currents (identifiability)	
a: I_{Na}	(1)
b: $I_{to,f}$	(0.99)
c: I_{CaL}	(0.99)
d: I_{bCl}	(0.93)
e: I_{K1}	(0.93)
f: I_{NaCa}	(0.88)
g: I_{NaK}	(0.42)
h: I_{ClCa}	(0.33)
i: $I_{to,s}$	(0.32)
j: I_{Kr}	(0.28)
k: I_{bCa}	(0.17)
l: I_{bNa}	(0.15)
m: I_{pCa}	(0.067)
n: I_{Ks}	(0.013)
o: I_{pK}	(0.0083)

Random stimulation →

Currents (identifiability)	
a: I_{Na}	(1)
b: I_{CaL}	(1)
c: $I_{to,f}$	(1)
d: I_{NaK}	(1)
e: I_{K1}	(0.99)
f: I_{NaCa}	(0.99)
g: I_{bCl}	(0.99)
h: I_{pCa}	(0.92)
i: I_{Ks}	(0.8)
j: I_{bCa}	(0.76)
k: I_{pK}	(0.71)
l: I_{bNa}	(0.65)
m: $I_{to,s}$	(0.64)
n: I_{ClCa}	(0.58)
o: I_{Kr}	(0.58)

Result - Random stimulation (O'Hara)





We can see that the perturbation effect H and identify index are increased

Currents (identifiability)	
a: I_{Na}	(1)
b: I_{Kr}	(0.91)
c: I_{CaL}	(0.78)
d: I_{to}	(0.67)
e: I_{NaK}	(0.2)
f: I_{NaCa}	(0.19)
g: I_{K1}	(0.14)
h: I_{bK}	(0.082)
i: I_{NaL}	(0.071)
j: I_{Ks}	(0.07)
k: I_{bNa}	(0.0086)
l: I_{bCa}	(0.0079)
m: I_{pCa}	(0.00026)

Random stimulation →

Currents (identifiability)	
a: I_{Na}	(1)
b: I_{to}	(1)
c: I_{K1}	(1)
d: I_{CaL}	(1)
e: I_{Kr}	(0.99)
f: I_{NaCa}	(0.98)
g: I_{NaK}	(0.97)
h: I_{bK}	(0.26)
i: I_{Ks}	(0.15)
j: I_{bCa}	(0.15)
k: I_{bNa}	(0.13)
l: I_{NaL}	(0.08)
m: I_{pCa}	(0.00081)

Conclusion

- It has developed a method for investigating the identifiability of the maximum conductance of ion channels in a model.
- Large singular values are associated with large perturbation effects along their corresponding singular vectors, while small singular values are associated with small perturbation effects.
- H is defined to measure perturbation effects on potential, which is especially useful when AP seemed to be visually identical.
- The identifiability index is made to measure the difference between the unit vector of the current and the projection of the unit vector to the unidentifiable space.
- Effect of time step: for the ten Tusscher model, the identifiability index of the I_{Na} current dropped
- Effect of drugs: few current identifiability index in Grandi and O'Hara model are affected.
- Effect of stimulation: random stimulation protocol can increase identifiability index

Conclusion

- This method is useful in the sense that it indicates how well blocking of individual currents can be identified using the model.
- For instance, that the AP model is very sensitive to changes in the sodium current. Then, if a sodium blocker is applied, such changes will be observed.

- But not all currents are identifiable, which indicates redundancy in the model in their ability to produce a single paced action potential (but not for random stimulus protocol).

- So, we might need model reduction to make it simpler in the future work.